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HAEMANGIOMAS OF THE ORBIT

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The authors describe their experience with systemic therapy of cavernous haemangiomas making use of interferon alpha. They have successfully used the method in treating two female patients with cavernous haemangiomas in the orbit.

In the first patient, the IFN therapy was followed by surgical removal of the tumour. In the second patient, surgical operation was not suitable. After the IFN therapy, the patient's state improved both subjectively and objectively.

Decreased level of bFGF in urine prove to be the criterion for successful treatment by IFN. The authors also stress the risk of complications in sucklings. When choosing the method of treatment, they emphasize the necessity of interdisciplinary cooperation.

INTRODUCTION

Vasoformative tissue tumours have been dealt with by experts from a wide range of medical disciplines owing to the relative frequency of the tumours, problematic diagnosis and, in many cases, complicated treatment. This refers in particular to large cavernous haemangiomas located in the proximity of major facial structures. Haemangiomas located in aesthetically important parts of the head can have an unfavourable effect on the growth and development of the face and they can also cause permanent facial deformities. The term "alarming" heamangiomas introduced by Enjolras[9] is used for slowly proliferating haemangiomas which can endanger the patients' life by damaging their vital functions and which are often accompanied by numerous complications (ulceration, bleeding, secondary infections).

Concerning the treatment of these tumours, one of the most delicate parts of the face is the orbit. Growing haemangiomas located in the orbit and periorbitally can cause exophthalmos. Deviation of the sight axis can result in purblindness. A very frequent complication of this is astigmatism caused by pressure on the eyeball or by the tumour spreading into the retrobulbar area. Loss of vision is an extreme complication which occurs if there is pressure on the optical nerve. All patients with haemangiomas located periorbitally should therefore undergo examination by an experienced ophthalmologist.

The pathogenesis of vasoformative tissue tumours has not been fully described to date. Nevertheless, during the past few years there has been remarkable progress owing to better scientific knowledge in the field of angiogenesis. The mechanism controlling growth and regression of haemangiomas is still not known, but the latest knowledge of pathophysiological angiogenesis is contributing to better understanding.

The life cycle of haemangiomas differs from most of tumours in their rapid proliferation followed by spontaneous regression. However, this is not always the case and, in contrast, some tumours permanently proliferate and prograde. For this reason it is necessary to commence therapy as soon as possible.

Over the past few years medicine has achieved notable progress in understanding the mechanisms of interferon therapy (IFN). A key role in the process is played by IFN receptors, classified as α, β and χ types. IFN binds itself to a specific receptor this triggers a cascade action initiating the transcription of IFN inducible genes. It is this gene expression that is responsible for the biological activity of interferons. Today we know that IFN inhibits angiogenic molecules. Such inhibitors are capable of penetrating into the finest capillaries of the blood system. An important role is also played by the basic fibroblastic growth factor (bFGF). When Ezekovitz *et al.*[10] exploited the angiogenic properties of interferon α-2a in the successful treatment of haemangiomas in new-born babies and sucklings, interferon become classified as an angiogenic inhibitor and it has become the most important method of treatment in cases of the "alarming" tumours.

OBSERVATION

At our clinic, we have succeeded in verifying the effect of IFN alpha on two patients with haemangiomas located in the orbit and periorbitally.

We treated a sixty-year-old female patient suffering from a large pulsing haemangioma in the left orbit and periorbitally. She had repeatedly underwent crystallization therapy in the department of ophthalmology of the University Hospital in Ostrava but without succes. The tumour kept on growing, its pulsation bothered the patient and due to its location it was narrowing the patient's field of vision (Fig. 1)

We performed CT examination with contrast material applied intravenously. On the CT scans we could observe hyperdense non-homogenous structures in the hypodermis of the superior rim of the left orbit, in the superior palpebra, and parabulbarly on the left side. (Fig. 2)

Owing to the risk of profusional bleeding during surgery we started systemic IFN alpha therapy. In the course of 4 weeks we applied 1–3 million units of Welferon s.c. three times a week. In the next series, we continued according to the Boston protocol (Table 1) up to a total dose of 55 million units of Welferon. Before and after the therapy the laboratory values and ECG were within the norm. Both subjective difficulties and pulsation receded and the tumour objectively reduced in size. (Fig. 3) In control arteriogram, made after completion of the treatment, we could clearly see the tumour regression (Fig. 4).

Table 1. Boston protocol (ref.[10])

Interferon alfa – 2b s.c. once daily:
1. Starting at 1×10^6 U/m^2/day
2. Increasing the dose after one week to 2×10^6/m^2/day
3. After a second week to the full dosage of 3×10^6/m^2/day

On the top of the orbit we could observe a small ball of a minute vascular anomaly. In both photographs, dilated venous convolutes in the venous phase in the left orbit were filled medially and cranially (Fig. 5, 6).

This presurgical preparation was followed by surgical intervention. Out of the arcuate section in the left ophrys we exstirpated a plum-sized tumour en bloc (Fig. 7). Histology confirmed the diagnosis of a cavernous haemangioma (Fig. 8, 9, 10). The patient has been problem free and without clinical signs of recurrence for 3 year. (Fig. 11).

The second patient was a 32-year-old woman, who came to our clinic because she felt unpleasant pressure and obnoxious pulsation in her left orbit. As a secondary clinical finding we established a diagnosis of cavernous haemangioma on the orbital floor (Fig. 12, 13). The degree to which the orbit had been affected was examined by selective arteriography of a. carotis interna on the left (Fig. 15). Due to the risk of damaging the optical nerve we did not operate on the patient. We decided to use systemic therapy by interferon alpha. During the first week we applied 1.5 mil. units of Welferon s.c. every second day; the second week 3 mil. units, also every second day. From the third week of treatment we continued according to the Boston protocol. Laboratory examination and ECG were within the norm. The application of 180 mil. units in three series was followed by MR examination (Fig. 16). As evident from the figure 16 (section T2) we observed on the laterodorsal wall of the orbit a hypersignalling, dense lesion.

The CT scans taken in the course of the treatment showed a hyperdense lesion in the form of a strip on the left. This lesion extended up to the optical canal. The tumour was smaller in comparison with the original finding (Fig. 14). The ophthalmogyric muscles in the right orbit were normal, but in the left orbit we could observe a small cavity. Figure 17 shows selective arteriography of the left external carotid artery. In comparison with the original arteriography the tumour reduced in size.

The clinical state of the patient is very good. The pain caused by pressure and pulsation is gone. We continue the interferon treatment according to the Boston protocol. We keep sklerotizing the haemangioma on the floor with Aethoxysclerol. (Fig. 18).

DISCUSSION

Haemangiomas are the most common of soft tissue tumours. They can be found in 5–10% of sucklings and in more than 20% of preterm infants. Despite their frequent occurrence, the pathogenesis of haemangiomas has not been fully described to date and the best form of therapy remains a controversial issue.

New methods of treatment, especially laser therapy and pharmacological inhibitors of angiogenesis, can significantly improve the patients' prospects where spontaneous regression has been insufficient and successive standard methods of treatment have failed.

Systemic treatment by interferon is indicated whenever surgical intervention is not suitable or in complicated cases, in which the tumour is resistant to other clinical methods, systemic steroid therapy in particular.[5, 20, 21] The treatment is especially appropriate in the case of "alarming haemangiomas" which express high proliferative activity and damage vital structures which concur life treatening complications.[8, 9, 14]

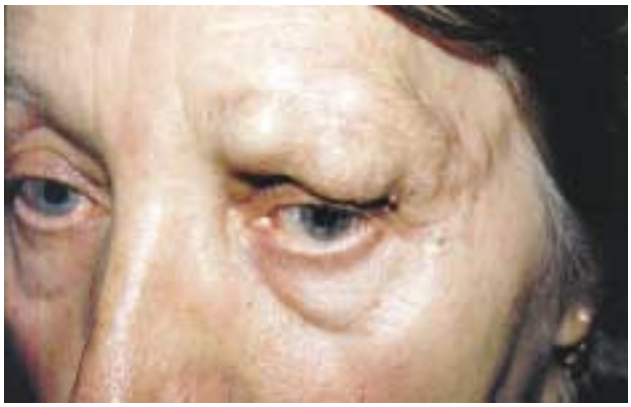

Fig. 1. 1st patient – haemangioma in the left orbit and periorbitally.

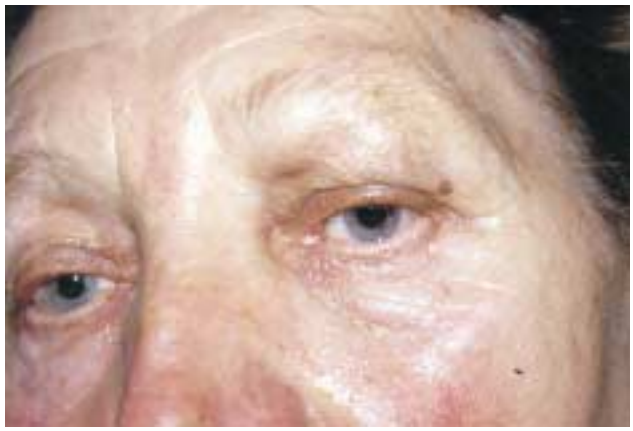

Fig. 3. State after systemic IFN alpha therapy.

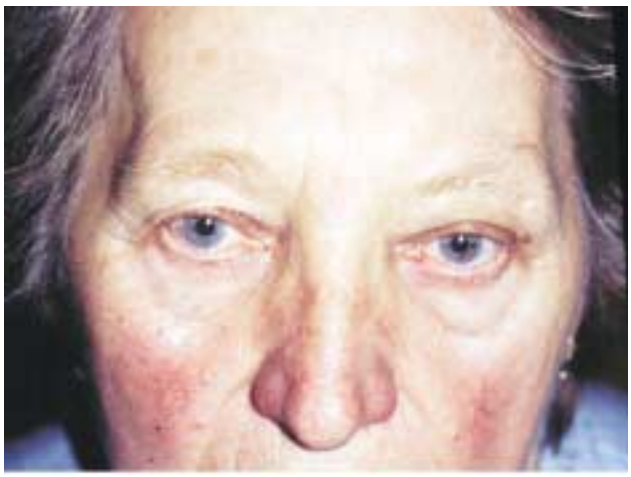

Fig. 11. State after IFN alpha therapy.

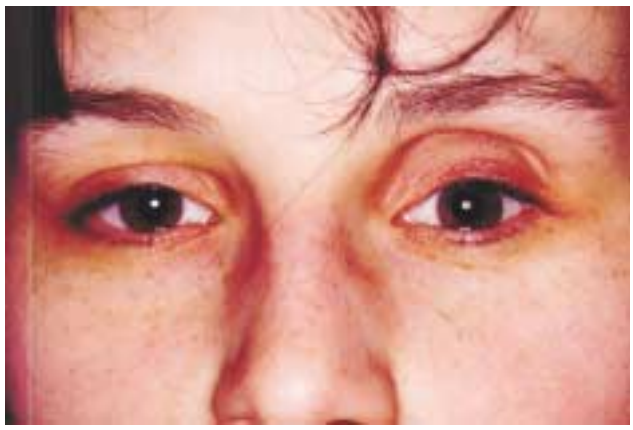

Fig. 12. 2nd patient – haemangioma in the left orbit.

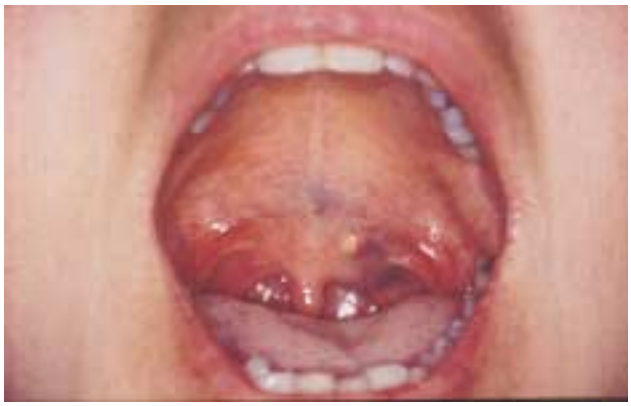

Fig. 13. Haemangioma on the orbital floor.

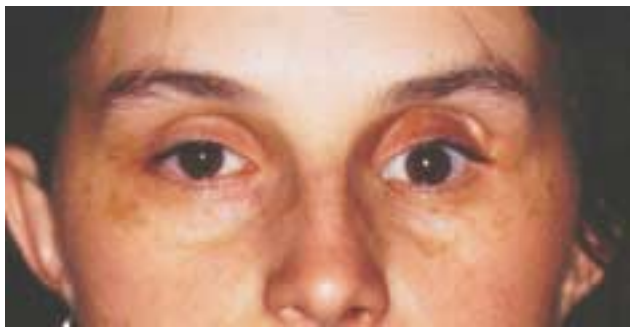

Fig. 18. State after IFN alpha therapy.

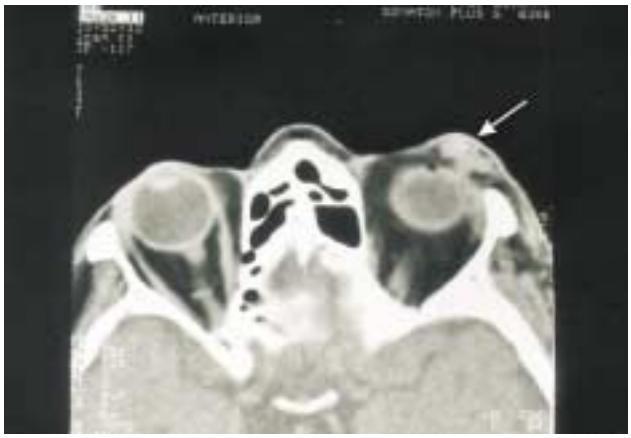

Fig. 2. CT1: CT examination of the orbit after application of contrastive substance intravenously shows hyperdense convolutes in the hypodermis pre- and paraorbitally on the left. The bulb remains intact.

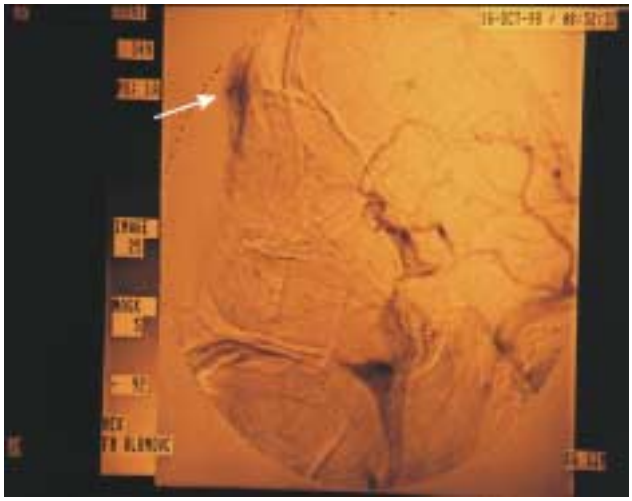

Fig. 4. Art. 1: angiography of the left carotid shows convolute of arteriovenous malformation in the venous phase periorbitally.

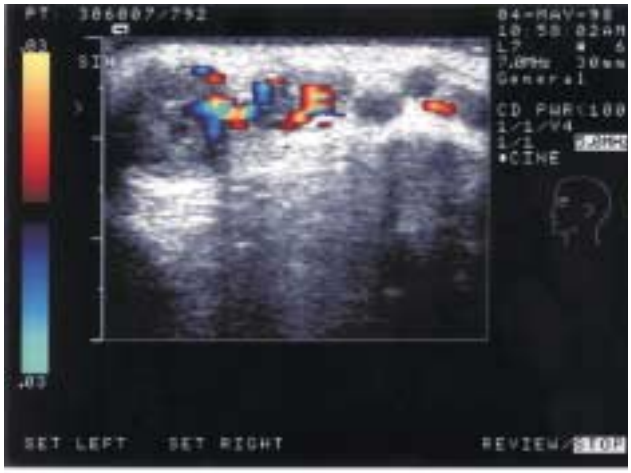

Fig. 5. Dopplerometric examination before IFN alpha therapy. Around the lesia (haemangioma) in the superior palpebra on the left there are several hypoechogenic spherical areas, lined by hyperechogenic tissue rich in blood supply.

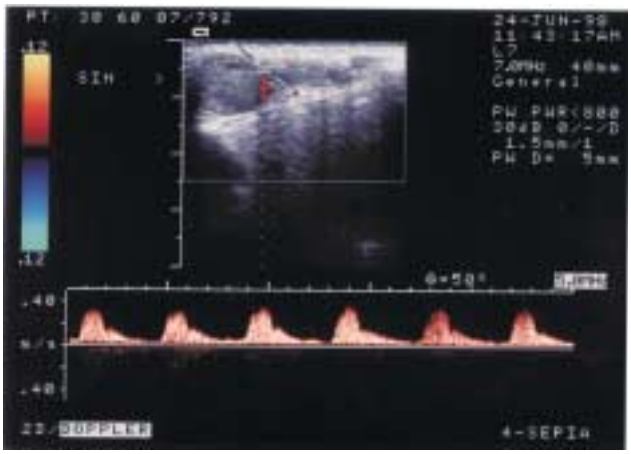

Fig. 6. Dopplerometric examination after IFN alpha therapy. The size of the body in the superior palpebra on the left remained unchanged. Its echogenity augmented and blood supply reduced significantly.

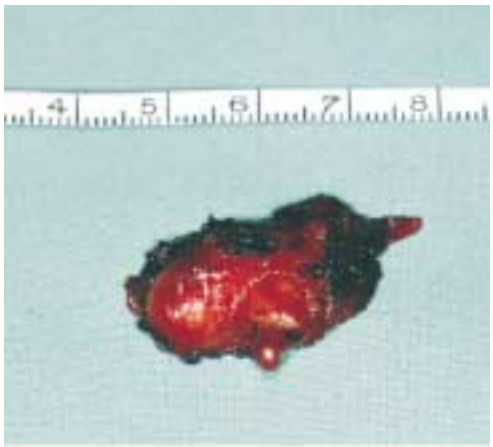

Fig. 7. Per operational preparation.

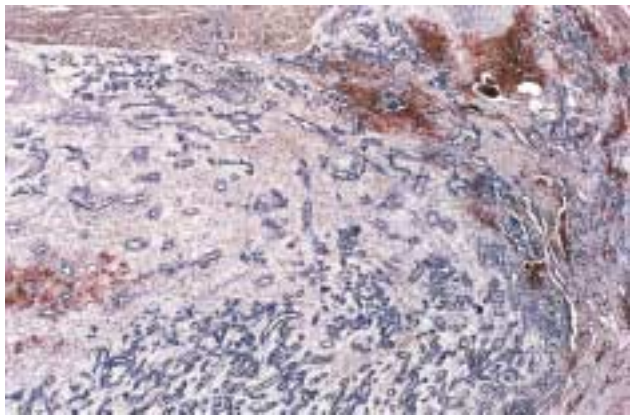

Fig. 8. Augmentation with several large blood-vessels surrounded by the haemangioma.

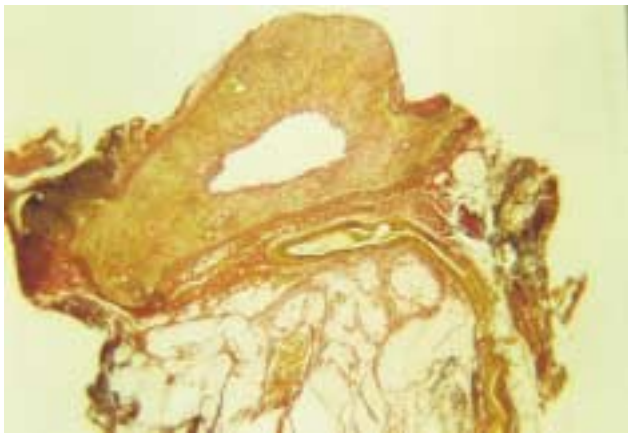

Fig. 9. Structure of a mixed haemangioma. Predominance of capillary constituents.

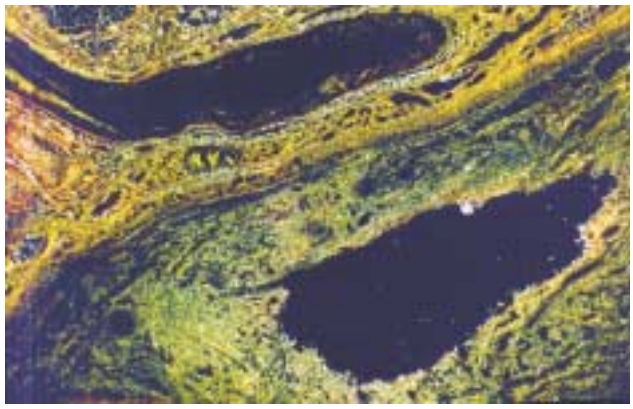

Fig. 10. Elastica with Van Gison – polarized light shows collagenized elements (apparent therapeutic effect).

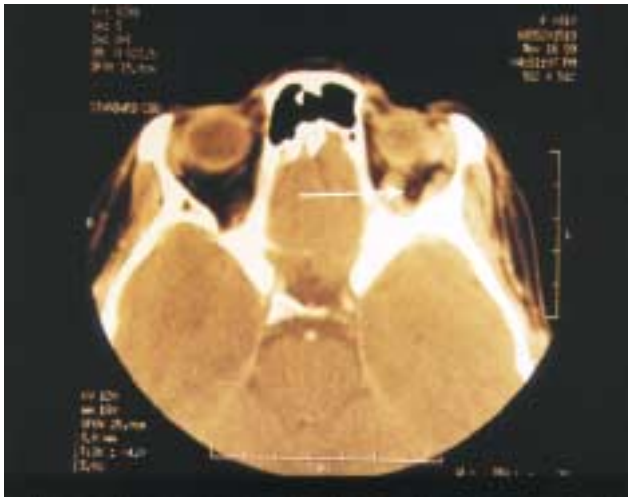

Fig. 14. CT1/CT examination of the orbit with contrastive substance applied intravenously shows convolute of venous malformation in the left orbit laterally from the bulb. The malformation continues along the lateral wall dorsally.

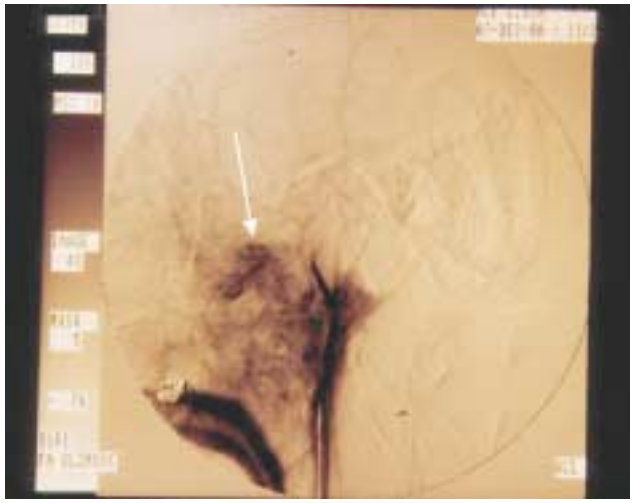

Fig. 15. Art1: selective angiography of the external carotid artery on the left proves a large finding in the facial area, stretching into the orbit. The finding corresponds with the structure of a haemangioma.

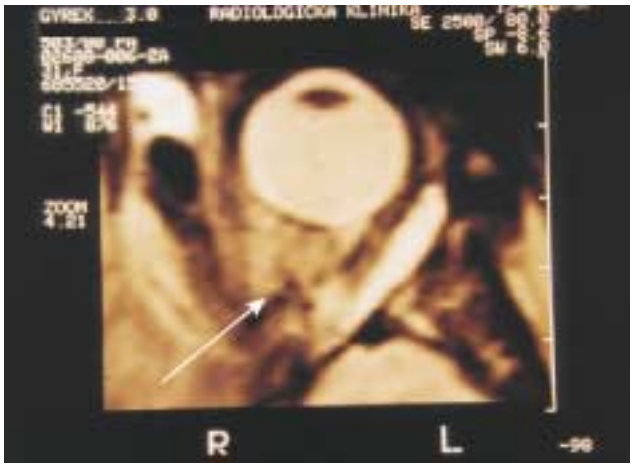

Fig. 16. MR1: MR of the orbit, transversal level, T2 weighted image of the left orbit laterodorsally shows a hyperintensive stripe stretching into the apex of the orbit.

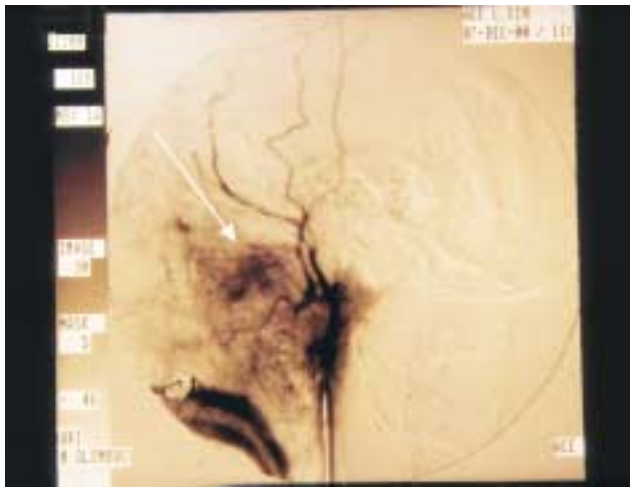

Fig. 17. Art2: control angiography of the external carotid artery proves reduction of venous dysplasia.

Interferon is particularly efficient when the orbit is concerned. Surgical intervention in the periorbital region risks reducing motility of the bulb or it can lead to blindness. The alternatives of medicaments treatment are considerably limited: the application of steroids directly into lesion is strictly contraindicated in the periorbital area due to risk of local damage to neurovascular structures.[4, 10]

In order to establish the diagnosis it is always important to consider the clinical appearance and common comprehensive arteriography which should be followed by selective or superselective angiography.

Over the past few years, research has shown that interferon alpha can inhibit angiogenesis through its indirect effect on urine bFGF. After a few weeks of interferon treatment, bFGF levels in urine lytically decrease together with a favourable clinical response. The increased level of bFGF in the patients' urine should therefore act as an important indicator for starting systemic interferon therapy.

Systemic application of IFN alpha is restricted to a certain extent by the side effects of the treatment. The appearance of the "flu syndrome", common after the introduction of the treatment, can be eliminated by the administration of paracetamol. The treatment is somewhat contraindicated in cases of cardiac insufficiency and epilepsy. Some patients suffer from headaches and myalgia in the course of the treatment.

The 50% therapeutic effect of IFN alpha in sucklings suffering from "alarming" haemangioma[3, 4, 10, 12, 20] has been verified a number of times. However, in 1998 Barlow *et al.*[1] described spasmodic diplegia as a serious complication of systemic IFN therapy, independent of treatment length. Drolet et al.[8] described this complication in as much as 20% of children (sucklings in particular). On the other hand, Deb et al. use their experience with systemic IFN alpha therapy in cases of the "alarming" haemangiomas to claim that the upper kinetic neuron is affected by benzyl alcohol, a preservative contained in some preparations. Clinical practice proves that appropriately chosen dosage frequency of interferons can considerably lower the risk of side effects.

The decision to use IFN therapy should result from a consensus among individual experts (oncologists, dental surgeons, paediatricians, dermatologists) and patients or young patients'. The method of treatment should be performed where possible to monitor effects, employing some of the specific cellular signs of angiogenesis (e.g. bFGF).

CONCLUSION

The treatment of haemangiomas using interferons requires good team cooperation. It is a long-term and expensive procedure. Nevertheless, appropriately chosen it can lead to notable results.

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